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13. ABSTRACT *(Maximum 200 words)*

The ARO Center of Excellence in Biotechnology was established within the Cornell University Biotechnology Program in 1986. The research focus of the Center was protein structure and function, with special emphasis on enzymes and receptors. Research projects funded through the Center represented a multidisciplinary attack on the molecular basis of how proteins and enzymes work, how energy and enzymic processes are coupled through cell membranes, how membrane receptors are used to transmit signals to the cell, and how signals are transmitted in the nervous system. The final report summarizes the results of the research.

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CENTER OF EXCELLENCE IN BIOTECHNOLOGY (RESEARCH)

FINAL REPORT

Dr. Milton Zaitlin
Biotechnology Program
Cornell University

19 February 1993

U. S. Army Research Office

Froposal No. 24629-LS-UIR
Contract No. DAAL03-87-K-0004

Office of Sponsored Programs
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Army Research Office
Center of Excellence in Biotechnology (Research)
Final Report
Grant No. DAAL03-87-K-0004
Proposal No. 24629-LS-UIR

1. Foreward

The ARO Center of Excellence in Biotechnology was established within the Cornell University Biotechnology Program in 1986. The research focus of the Center was protein structure and function, with special emphasis on enzymes and receptors. Research projects funded through the Center represented a multidisciplinary attack on the molecular basis of how proteins and enzymes work, how energy and enzymic processes are coupled through cell membranes, how membrane receptors are used to transmit signals to the cell, and how signals are transmitted in the nervous system.

The Center was governed by a Scientific Administrative Board comprised of representatives from the faculty and the Biotechnology Program's industrial sponsors. Specific research projects supported by the Center were chosen on a competitive basis from proposals submitted by faculty members to this Board. Five Program Project Grants which represented the main focus of the Center were established. These multidisciplinary grants involved twenty-six Cornell faculty representing ten University Departments. Since the recruitment of new faculty to Cornell University was crucial for the success of the Biotechnology Program, special new investigator grants were awarded, on a competitive basis, to seven new faculty members. In addition, thirty-seven individual and/or collaborative projects were funded and twelve graduate student fellowships were awarded a final year from the Center.

In total, more than 67 Cornell faculty and more than 100 other researchers were involved in ARO Center projects (approximately 25% of the other researchers received some salary support from the grant). Approximately half of the 80 students on the personnel listing received their degrees while working on an ARO project.

The Center's research support facilities were subsidized by funds from the ARO grant. Services ranging from monoclonal antibody production to peptide synthesis were provided to members of the Cornell community, as well as other educational institutions and businesses in New York State. These facilities also served as the basis for our strongest continuing interactions with Army personnel.

During the course of this grant, two inventions were disclosed. The first, "Site-specific endonuclease, I-Ppo, as a tool in genomic mapping and genetic engineering" (Drs. V.M. Vogt and D. Muscarella) has been licensed to Promega and is being marketed. The second disclosure "Automated, multicompartmental cell culture system" involves Drs. M. Shuler and J. Babish and graduate student L. Sweeney.

4. A. Statement of the Problem

The Center undertook a multidisciplinary attack on the molecular basis of how proteins and enzymes work, how energy and enzymic processes are coupled through cell membranes, how membrane receptors are used to transmit signals to the cell, and how signals are transmitted in the nervous system. Sophisticated biochemical, genetic, chemical, engineering and instrumental techniques were utilized. Center funded research concentrated on Protein Structure and Function, with subcategories of Enzymes and Receptors.

4. B. Summary of the Most Important Results

(A complete list of individual and collaborative projects receiving support from the ARO Center grant follow this summary. Detailed final reports on all individual research projects are available in the Biotechnology Program Office and will be furnished upon request.)

Considerable emphasis was placed on studies of the nicotinic acetylcholine receptor, an important protein involved in the facilitation and regulation of signal transmission between cells of the nervous system and at the neuromuscular junctions. It has been implicated in several diseases, and interacts with insecticides, toxins, and many clinically important compounds, such as tranquilizers, antidepressants, and anesthetics. In this program, the mRNAs for the muscle and neuronal types of the receptor have been expressed in yeast, and have shown to exhibit function. The allosteric site on the acetylcholine receptor has been identified. Additionally, inactive precursors of carbamoylcholine, a stable analog of acetylcholine have been synthesized. They were photolyzed to release carbamoylcholine on the sub-millisecond time scale, and they have been used in chemical kinetic measurements of receptor function in neuronal PC12 cells, muscle BC_3H1 cells and Xenopus oocytes.

Another principal area of research centered on understanding the molecular mechanisms underlying multi-component receptor-coupled signal transduction. Two classes of signaling systems received primary emphasis; one involved growth factor-stimulated mitogenesis, the other involved receptor-mediated signaling in the immune response (with the model being immunoglobulin E [IgE]-stimulated histamine release). The epidermal growth factor receptor was found to be fully functional as a tyrosine kinase in the monomeric state, but apparently undergoes dimerization as a signal for receptor processing. A new ras-like GTP-binding protein was discovered; it is the human homolog of a yeast cell-division cycle protein, and appears to play a role in `trafficking' growth regulatory molecules to different parts of cells, as an outcome of epidermal growth factor regulation. In addition, a potentially new class of mitogenic receptors was discovered that bind ATP (as a mitogen) and stimulate endothelial cell growth substantially, through the actions of pertussis toxin-sensitive GTP-binding proteins.

Using both natural epidermal growth factor and mutants derived by recombinant DNA methods, the three-dimensional structure of the protein was determined, using 2D NMR. For these studies an efficient Bacillus brevis expression system was developed to produce large quantities of both wild-type and mutant growth factors. A new NMR pulse procedure was developed to facilitate the acquisition of data in aqueous solution. Recently heteronuclear NMR spectroscopy (with ^{15}N-substituted proteins) was used to determine the three-dimensional structure of transforming growth factor alpha. Both this factor and the epidermal growth factor bind to similar receptors in the cell.

At least five different GTP-binding proteins were shown to be involved in mediating IgE-stimulated second messenger changes, including increases in intra cellular Ca^{++}. The IgE receptor was shown to stimulate the tyrosine phosphorylation of distinct cellular proteins, via the activation of members of the src family of tyrosine kinases. During the course of these studies, a remarkable number of analogies between the signaling pathways initiated by growth factors and immunoglobulins was discovered.

A number of projects studied the folding and structure of several proteins. In collaboration with a visiting scientist from the Natick Laboratory, the structure of a simple model of silk was computed. Studies on the enzyme DNA photolase from E. coli (which can reverse the lethal and mutagenic effects of UV light on the bacterium), have helped elucidate the mechanism of this important enzyme. Other enzymes for which enzyme mechanisms were investigated include thiamine pyrophosphate and chorismatic mutase, which catalyzes the rearrangement of chorismic acid to prephenic acid in the first committed step to the synthesis of phenylalanine and tyrosine. NMR and X-ray crystallographic studies have been carried out on monofunctional mutase, and on cellulase E_2 from the T. fusca.

Several studies were focused on the binding of proteins to regulatory sites on nucleic acids. UV-mediated cross linking was the most effective tool for mapping the location of proteins on DNA. Proteins which bind to the telomeric DNA were characterized, as well as those which involved the interaction of the phage lambda Q protein with lambda DNA. A novel new method was developed to increase the efficiency with which yeast mitochondria could be transformed.

LIST PROJECTS RECEIVING SUPPORT FROM THE ARO CENTER GRANT 1986-1992

Program Project Grants

"Interactions of Proteins with Regulatory Sites on Nucleic Acids"

J. Calvo, T. Fox, J. Lis, J.W. Roberts and B.-K. Tye 1987-89
B.-K. Tye, T. Fox, J. Lis, J.W. Roberts and T. Begley 1989-90

"Receptor-signaling Mechanisms"

R. Cerione, B. Baird, C. Fewtrell, L. Heppel, W. Webb and E. Racker 1987-92

"Development of Embryo Stem Cell Technology for Production of Chimeric Rabbits and Cattle"

W. Hansel, R. Foote, W. Mark and D. Antczak 1989-90

"Investigations of the Nicotinic Acetylcholine Receptor"

G. Hess, O.P. Hamill, R.E. Oswald, M. Salpeter and G.A. Weiland 1987-89
G. Hess, O.P. Hamill, R.E. Oswald, T. Podleski, M. Salpeter and G. Weiland 1989-92

"Protein Folding and Assembly: Studies on the Mechanism, Function Design and Inhibition of Enzymes"

H. Scheraga, B. Ganem, T. Begley, D. Wilson and R.E. McCarty 1987-89
H. Scheraga, B. Ganem, T. Begley, D. Wilson and P.A. Karplus 1989-92

New Investigator Grants

R.A. Cerione 1987-89
"The Role of Non-Tyrosine Kinase Growth Factor Receptors in Neuronal Development and in the Immune Response"

P.A. Karplus 1989-91
"X-ray Structure Determination of Ferredoxin: NADP+ Reductase"

J.W. Casey 1989-91
"Delineation of Retroviral Regulatory Pathways that Serve as Potential Targets for Antiviral Activity"

R.B. Silver 1989-91
"Single Photon Video Microscopic Imaging of the Calcium Ion Fluxes that Regulate the Onset of Mitosis and 3-Dimensional Stereoscopic Reconstruction of Dividing Cells"

Y.-F. Chang — 1990-92
"Species Specificity of Pasteurella Leukotoxin to Mammalian Cell Surface"

V. Meyers-Wallin — 1990-92
"Genetic Control of Testis Development in Embryos having a Female Chromosome Constitution"

A. Panagiotopoulos — 1990-92
"Thermodynamics of Protein Denaturation Using a Novel Experimental Approach"

Individual and/or Collaborative Projects 1986-1992

D.M. Antczak, L.E. Carmichael and W. Rebhun — 1986-87
"Genetic and Viral Interactions in Tumor Development"

R.A. Cerione — 1986-87
"Structure-Function Studies of Growth Factor Action"

C. Fewtrell and L. Nowak — 1986-87
"Electrophysiological Identification of the IgE Receptor-Activated Calcium Channel of Mast Cells"

L.A. Heppel — 1986-87
"Identification of the Receptor for Extracellular ATP in Quiescent Cultures of Mammalian Cells"

G.P. Hess — 1986-87
"Chemical Kinetic Measurements of Receptor Function on Cell Surfaces with a μSec Time Resolution"

R.E. McCarty — 1986-87
"Characterization of Chloroplast F_O"

L.M. Nowak — 1986-87
"The Effects of cGMP on Excitatory Amino Acid Receptor/ Channels in Purkinje Neurons"

R.E. Oswald — 1986-87
"Structure and Function of an Allosteric Site on Acetylcholinesterase"

T. Podleski and M.M. Salpeter — 1986-87
"Studies on the Role of Ascorbic Acid in Regulating Acetylcholine Receptor Synthesis *in vitro*"

E. Racker — 1986-88
"Stimulation of Phosphoinositol Turnover by Growth Factors and Modulation of Receptors by Phosphorylation"

W.W. Webb — 1986-88
"Do Ion Channel Conductance Fluctuations Reflect Conformational Dynamics of Membrane Proteins?"

D.F. Antczak and J.A. Appleton — 1987-89
"Advanced Techniques in Monoclonal Antibody Production"

C.A. Batt and S. Zahler "Strategy for the In Vivo Genetic Engineering of Enzymes"	1987-89
M. Salpeter and L. Nowak "Amino Acid Receptor Distribution on Developing Purkinje Neurons"	1987-89
G. Weiland and W.A. Horne "The Use of Monoclonal Antibodies in Purification and Characterization of the Voltage Sensitive Calcium Channel"	1987-88
G. Hess and W.W. Webb "Optical Recognition and Monitoring of Receptor Activity in Cells"	1988-89
H.A. Scheraga, G. Nemethy and R. Wu "Genetic Engineering of Protein Structure and Function Based on Theoretical and Experimental Analysis and Design of Protein Structure"	1988-90
A.P. Bretscher and T.C. Huffaker "AFAS: Affinity Filter Activity Screening"	1989-90
B.J. Cooper and R.J. Avery "Molecular Characterization of X-Linked Muscular Dystropny in the Dog"	1989-91
C.C. Chu, J.A. Marsh and M. Appel "In Vitro Study of the Effect of Electric Current on the Release of Fibroblast Growth Factor of Alveolar Macrophages"	1989-90
D.A. Hammer and B.U. Pauli "Measurement of the Attachment of Metastatic Tumor Cell Lines to Organ-Specific Endothelial Cells in a Parallel Plate Flow Chamber Assay"	1989-91
A. Yen and J. Blue "c-myc Oncogene and Rb Anti-oncogene Products: Their Role in Progression of Myeloid Leukemia in an Animal Model With and Without Treatment with the Differentiation Inducing Agent, Retinoic Acid"	1989-91
R. Avery, F. Noronha and D. Usher "Inhibition of Feline Leukemia Virus Gene Expression by Antisense RNA"	1990-91
A. Bass "Spatial-Temporal Organization of Vertebrate Neuromuscular Systems"	1990-91
B. Ganem and J. Henion "Mass Spectrometric Detection of Covalently Bound Intermediates in Enzymatic Reactions"	1990-92
J. Henion "Instrumentation Development: Mass Spectrometry of Proteins and Nucleic Acids"	1990-92
P. Hinkle and D. Wilson "Expression of a Human Glucose Transporter in E. Coli"	1990-92

R. Roush, R. Constant and R. MacIntyre 1990-91
"Isolation of Insecticide Resistance Genes as Markers for the Cloning of Nerve Cell Receptors"

M. Shuler and J. Babish 1990-92
"Cell Culture Animal Analogs for Toxicity Testing - Application to Naphthalene Toxicity"

M. Suter and E. Keller 1990-92
"Molecular Cloning of cDNA of a Keratinocyte Membrane Receptor Recognized by Pemphigus Autoantibody"

V. Vogt and T.C. Huffaker 1990-92
"An Intron-Encoded Endonuclease with Potential Use in Genomic Mapping"

R. Cerione and P.A. Karplus 1991-92
"Structural Studies of Transducin, the G Protein Responsible for Vision"

D. Hammer and W. Olbricht 1991-92
"Relationship Between Cell Surface Chemistry and Cell Aggregation Studies-2 Cell System"

J. Helmann and S. Zahler 1991-92
"Iron Regulation of Gene Expression in Bacillus Subtilis"

B.U. Pauli and Y.-F. Chang 1991-92
"Cloning a Lung Endothelial Cell Adhesion Molecule that Mediates Melanoma Lung Metastasis"

Graduate Fellowships (the following students began fellowship support under our ARO fellowship grant (DAAL03-86-G-0204) and completed a final year on the Center of Excellence Grant.

Fellow: Ingrid Brust-Moscher Advisor: Watt W. Webb
Project Title: "Motor Molecules in Cellular Microlocomotion"
Summary: This study of cellular microlocomotion using fish keratocytes addressed first whether the membrane motion is active or passive. The objective being to distinguish between three proposed models for cell locomotion: the retrograde membrane flow model, the tank track model and the passive membrane model.

Fellow: Joseph Henderson Advisor: David M. Soderlund
Project Title: "Cloning and Characterization of Putative GABA Receptor Gene in *Drosophila*"
Summary: The overall objective of this work is to achieve a more complete characterization of the PCR-derived clone that appears most like to be part of the insect GABA receptor gene(s). Specific objectives are (1) structural characterization of the gene by obtaining the complete cDNA and genomic DNA and sequencing them, and (2) functional characterization of the gene product by expression in *Xenopus* oocytes. In the past year we have cloned and sequenced fragments of two more putative ligand-gated chloride channel genes from *Drosophila*, bringing our total to three. Current work is aimed at further characterization of these three clones.

Fellow: Franklin Moy Advisor: Harold Scheraga
Project Title: "Structure-Function Studies of Growth Factors and Their Analogues"

Summary: A method for overcoming solvent-saturation transfer and preirradiation-associated spin-diffusion effects in aqueous solutions using frequency-shifted shaped pulses was developed. This method was applied to study human transforming growth factor alpha (hTGFα) at various pH and temperature conditions. Heteronuclear NMR studies were carried out on hTGFα at neutral and acidic pH to compare the structure and dynamics at the two pH conditions. The solution structure was determined by NMR spectroscopy and refined by energy minimization with restraints.

Fellow: Julio J. Mulero Advisor: Thomas D. Fox
Project Title: "Translational Initiation of the Yeast Mitochondrial mRNA for Cytochrome c Oxidase Subunit II"

Summary: This project is undertaken to understand the control of yeast mitochondrial gene expression. We have found some very exciting information about how the yeast nuclear gene, PET111 activates the expression of the mitochondrial gene, COX2. We have found strong indications that the PET111p specifically activates translation of the COX2 mRNA through a site at the 5'-UTR.

Fellow: Renee Reijo Advisor: Tim C. Huffaker
Project Title: "Structure and Function of Proteins of the Mitotic Spindle in Yeast"

Summary: Study of r254, a gene believed to be involved in microtubule function in yeast has moved from a genetic study of its mutant phenotype to a molecular characterization of the gene. Basic experiments, including identification, cloning and sequencing, eliminating the gene from wild type yeast cells, overexpressing the gene, and raising antibodies against the protein have been completed. Current experiments are designed to determine localization of the r254 protein in yeast cells.

Fellow: Michael L. Spezio Advisor: David B. Wilson
Project Title: "Three Dimensional Structure of the Catalytic Unit of Cellulase E2"

Summary: We have succeeded in determining the structure of the catalytic domain of a highly active cellulase. A manuscript describing this work is in preparation. In addition, we have identified the active site of this enzyme by binding the ligand cellobiose to the enzyme in the crystal and determining its binding site by difference Fourier methods. We have tentatively identified several amino acid residues as being involved in binding and hydrolyzing cellulose. Plans are underway to utilize these results to guide the protein engineering of enhanced catalytic activity into this cellulase.

Fellow: Grace A. Stafford Advisor: Gregory A. Weiland
Project Title: "Regulation of L-type Voltage Dependent Calcium Channels"

Summary: After initial encouraging results in the calcium channel project, a series of roadblocks caused a change in the project. Since the Weiland laboratory had interest in nicotinic acetylcholine receptor/ion channel complex (nAChR) Ms. Stafford prepared to express neuronal nAChR in Xenopus oocytes to study the interaction of the receptor and Substance P (SP), a neuropeptide. It has now been demonstrated that acetylcholine induces currents in oocytes expressing the nAChR and that the currents are attenuated by SP. Attempts will be made to elucidate further the mechanism of interaction.

Fellow: Lisa M. Sweeney Advisor: Michael L. Shuler
Project Title: "Cell Culture Animal Analogs for Toxicity Testing--Applicatiuon to Naphthalene Toxicology"

Summary: In our previous work with the cell culture analog system, we demonstrated that two different cell types may be maintained in momolayer culture in a system with recirculated media. More recently we have successfully operated a hollow fiber unit in place of one of the tissue culture bottles. This substitution allows a substantial decrease in the total volume of medium used and demonstrates the modularity and flexibility of the cell culture analog system.

In future experiments, naphthalene toxicology will be studied in the cell culture analog system.

Fellow: Linda Templeman Advisor: Daniel A. Hammer
Project Title: "Quantitation of Receptor-MediatedCell Adhesion Using a Parallel-Plate Flow Chamber Assay"

Summary: Receptor-mediated cell adhesion under conditions of flow is an extremely important component of many physiological and biotechnological processes. We have built a parallel-plate flow chamber in order to observe the dynamics of cell rolling on a ligand-coated substrate in a well-defined fluid flow. We covalently attach the ligands of interest via a bifunctional linker to a thin polyacrylamide gel which is placed in this flow chamber. Our experiments use the rat basophilic leukemia cell (RBL) a model cell line which will allow us to measure the relationship between cell-surface chemistry and adhexiveness. Videomicroscopy interfaced with an image analysis system is used to determine the average velocity and percent adhexion of cells for a given set of experimental conditions. We shall compare our experimental results with our current model predictions and will refine our models to reflect observed phenomena.

Fellow: Michael Ward Advisor: Daniel A. Hammer
Project Title: "Biophysical Studies of the Morphology and Strength of Attachment of Insect Cells to Ligand-Coated Surfaces"

Summary: We have developed a detailed mathematical model which examines the role of focal contacts on the strength of receptor-mediated adhesion to ligand-coated surfaces. This work has been submitted to Biophysical J. for publication. Currently, we are seeking to extend this model to the time-dependent detachment of a cell from a ligand-coated substrate. Additionally, we are finishing an investigation of the effect of specific chemical and physical factors on cell-substrate interface morphology. We find that under certain conditions, the cell membrane forms wave-like structures which give rise to isolated clusters of adhesion receptors. These clusters are believed to play an important role in focal contact formation and signal transduction.

Fellow: Salli A. Wood Advisor: William J. Brown
Project Title: "Investigating theRegulation of Cell Surface M6P/IGF-II Receptor Expression Using the Drug Brefeldin A"

Summary: We have found that brefeldin A (BFA) induces the formation of an extensively fused network of membranes derived from the *trans* Golgi network (TGN) and early endosomes (EE). We have demonstrated the unaffected passage of endocytosed material through the fused TGN/EE compartments to lysosomes in BFA-treated cells. We also confirmed that BFA caused the formation of tubular lysosomes, although the kinetics and extent of tubulation varied greatly between different cell types. Our results show that BFA has multiple, profound effects on the morphology of various compartments of the endosome-lysosome system. In spite of these changes, endocytic traffic can continue through the altered compartments suggesting that transport occurs through non-coated vesicles or through vesicles that are insensitive to BFA.

Fellow: William Yarnell Advisor: Jeffrey Roberts
Project Title: "The Molecular Mechanism of Antitermination: Interactions of Lambda Q Protein with a Paused Transcription Complex"

Summary: We have characterized physically, for the first time, the site in DNA where the Q antiterminator protein binds, by protection against both exonuclease digestion and the DNA-cleaving agent MPE. We have demonstrated important effects of mutants affecting Q function on the structure of the complex. These experiments have led to specific models of the way the antiterminator proteins affect the elongation properties of RNA polymerase. This work has been described in: W.S. Yarnell and J. W. Roberts (1992) "The Phage Lambda Gene Q Transcription Antiterminator Binds DNA in the Late Gene Promoter as it Modifies RNA Polymerase" Cell 69, 1181-1189.

Research Support Facilities

Video Imaging Facility	C. Fewtrell	1987-88
Flow Cytometry and Cell Hybridization	D. Antczak	1987-89
Amino Acid Analysis, Sequencing & Oligonucleotide Synthesis	H. Scheraga	1987-88
Plant Tissue Culture Facility	E. Earle	1987-88

In 1988, the Biotechnology Program's Research Support Facilities were moved to the new Biotechnology Building and personnel were hired to direct each user laboratory as follows.

Peptide/DNA Synthesis and Analysis	T. Thannhauser	1988-92
Computer and Molecular Graphics	M. Schrier	1988-92
Flow Cytometry and Video Imaging	J. Slatery	1988-92
Plant Tissue Culture and Transformation Facility	K. Kindle	1988-92
Fermentation Facility	D. Wilson	1988-92
Monoclonal Antibody Facility	M. Noden	1988-91

A pamphlet describing the services offered by each of the above facilities is included in the Appendix to this report.

The Biotechnology Program's Research Support Facilities listed above are frequently used by a number of Army researchers from Natick, Walter Reed and Aberdeen.

Technical Reports Submitted to the Army Research Office

Semi-annual progress Reports were submitted to the Army Research Office beginning with the period 1 January 1987 thru 30 June 1987 and ending with 1 January 1992 thru 30 June 1992.

4. C. Publications

D.F. Antczak and W.R. Allen (1988). "A Non-Genetic Developmental Defect in Trophoblast Formation in the Horse: Immunological Aspects of a Model of Early Abortion." Pp. 123-140. In Early Pregnancy Loss: Mechanisms and Treatment. Proc. 18th Study Group of the Royal College of Obstetricians and Gynaecologists, October 1987 (R.W. Beard and F. Sharp, eds). Peacock Press, Ashton-under-Lyne, Lancs., England.

R.A. Cerione, S. Kroll, R. Rajaram, C. Unson, P. Goldsmith and A.M. Spiegel (1988) "An Antibody Directed Against the Carboxyl-Terminal Decapeptide of the α Subunit of the Retinal GTP-Binding Protein, Transducin: Effects on Transducin Function." J. Biol. Chem., 263, 9345-9352.

M. C.Costanzo and T. D. Fox (1988) "Transformation of Yeast by Agitation with Glass Beads", Genetics, 120, 667-670.

A.L.Crump, W. Davis and D.F. Antczak, (1988). "A Monoclonal Antibody Identifying a T-cell Marker in the Horse." Animal Genetics 19, 207-215.

W.L.Donaldson, A.L. Crump, C.Zhang, J. Kornbluth, M. Kamoun, W. Davis and D.F.Antczak (1988). "At Least Two Loci Encode Allotypic Class I MHC Antigens in the Horse." Animal Genetics 19, 195-206.

F.A. Gonzalez, D.J. Gross, L.A. Heppel, and W.W. Webb (1988). "Studies on the Increase in Cytosolic Free Calcium Induced by Epidermal Growth Factor, Serum, and Nucleoides in Individual A431 Cells." J. Cell. Physiology, 135, 269-276.

F.A. Gonzalez, L.A. Heppel, D.J. Gross, W.W. Webb and G. Parries (1988). "The Rapid Desensitization of Receptors for Platelet Derived Growth Factor, Bradykinin and ATP: Studies on Individual Cells Using Quantitative Video Fluorescence Microscopy." Biochem. Biophys. Res. Commun. 151, 1205-1212.

W.A. Horne, M. Abdel-Ghany, E. Racker, G.A. Weiland, R.E. Oswald, and R.A. Cerione (1988). "Functional Reconstitution of Skeletal Muscle Ca^{2+} Channels: Separation of Regulatory and Channel Components." Proceedings of the National Academy of Sciences 85: 3718-3722.

J. Krupinski, R. Rajaram, M. Lakonishok, J.L. Benovic, and R.A. Cerione (1988) "Insulin-dependent Phosphorylation of GTP-Binding Proteins in Phospholipid Vesicles", J. Biol. Chem., 263, 12333-12341.

M. Kubina, P.J. Millard and C. Fewtrell (1988) "Comparison of Free Cytoplasmic Ca^{2+} Changes Monitored with Aequorin and Fura-2 in RBL-2H3 cells." Fourth Congress of Cell Biology.

S. Lazary, D.F. Antczak, E. Bailey, T.K. Bell, D. Bernoco, G. Byrns, and J. McClure (1988). Joint Report of the Fifth International Workshop on Lymphocyte Alloantigens of the Horse. Animal Genetics 19.

P. Millard, T. Tyan, W. Webb and C. Fewtrell (1988). "Digital Video Fluorescence Imaging of Free Cytoplasmic Ca^{2+} in Tumor Mast Cells Stimulated with Soluble and Immobilized Antigen." Fourth International Congress of Cell Biology.

P.J. Millard, D. Gross, W.W. Webb and C. Fewtrell (1988). "Imaging A synchronou Changes in Intracellular Ca^{2+} in Individual Stimulated Tumor Mast Cells." Proc. Natl. Acad. Sci. USA, 85, 1854-1858 (March).

G. T. Montelione, K. Wuthrich and H. A. Scheraga (1988) "Sequence-specific 1H NMR Assignments and Identification of Slowly Exchanging Amide Protons in Murine Epidermal Growth Factor", Biochemistry, 27, 2235-2243.

V. Narasimhan, D. Holowka, C. Fewtrell and B. Baird (1988) "Cholera Toxin Increases the Rate of Antigen-Stimulated Calcium Influx in Rat Basophilic Leukemia Cells", J. Biol. Chem., J. Biol. Chem., 263, 19626-19632.

W.J. Phillips, and R.A. Cerione (1988) "The Intrinsic Fluorescence of the α Subunit of Transducin: Measurement of Receptor-Dependent Guanine Nucleotide Exchange." J. Biol. Chem., 263, 15498-15505.

P. Ray, F. J. Moy, G. T. Montelione, J. F. Liu, S. A. Narang, H. A. Scheraga and R. Wu (1988) "Structure-Function Studies of Murine Epidermal Growth Factor: Expression and Site-Directed Mutagenesis of Epidermal Growth Factor Gene", Biochemistry, 27, 7289-7295.

T.A. Ryan, J. Meyers, D. Holowka, B. Baird and W.W. Webb (1988). "Molecular Crowding on the Cell Surface." Science 239, 61-63.

T.A. Ryan, P. Millard, C. Fewtrell and W.W. Webb (1988). "Dynamics of Cytosol Ca^{2+} in Tumor Mast Cells Induced by Antigen Stimulation with Mobile and Localized Antigens." Biophys. J. 53, 353a.

M. P. Weiner, T. W. Thannhauser, J. H. Laity, M. E. Benning, D. P. Lee and H. A. Scheraga (1988) "Plasmic Purification Using Reverse-Phase High Performance Liquid Chromatography Resin PRP", Nucleic Acids Res., 16, 8185.

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5. REPORT OF INVENTIONS:

A. Site-specific endonuclease, I-Ppo, as a tool in genomic mapping and genetic engineering.

B. Automated, multicompartmental cell culture system.